REMARKS/ARGUMENTS

This application has been amended in a manner that is believed to place it in condition for allowance at the time of the next Official Action.

Claims 1-28, 30-41, and 44 have been canceled. New claims 45-60 have been added. Support for new claims 45-60 may be found generally throughout the specification and in original claims 1-11 and 21-27, respectively.

In the outstanding Official Action, the specification was objected to for allegedly not reciting all the required sequence identification numbers as required under 37 CFR §1.821(d). Upon reviewing the specification and claims, applicants note that page 40 was amended in the amendment of October 29, 2001. Moreover, applicants believe that the claims have been drafted in a manner so that the proper sequence identification numbers are recited.

However, upon reviewing the present specification, it is apparent that the sequences set forth on page 11 only illustrate the microdeletions in the *GH1* gene causing GH deficiency and short stature. For example, the lower case letter set forth in the sequence is to delete a base. As a result, applicants do not believe that the sequences are capable of being characterized in such a manner.

The outstanding Official Action also objected to the disclosure for containing an embedded hyperlink. The embedded hyperlink found on page 38 has been deleted. Thus, it is believed that the present application satisfies the requirements of MPEP §608.01.

In the outstanding Official Action, claims 1-11 and 21-27 were rejected under 35 USC 112, first paragraph, for allegedly being based on a non-enabling disclosure. It is believed that the present amendment obviates this rejection.

The outstanding Official Action states that the specification is enabling for methods for detecting a variation in the *GH1* nucleic acid. However, the outstanding Official Action alleged that the present disclosure does not enable methods for detecting a variation in *GH1* effective to act as an indicator of a GH dysfunction in an individual or methods of identifying individuals having GH disfunction.

In imposing the rejection, the outstanding Official Action states that the specification teaches improved methods for identifying mutations in the *GH1* gene, wherein the method comprises comparing the sequence of a *GH1* nucleic acid from a test sample with a standard *GH1* nucleic acid sequence. The outstanding Official Action states that while 54 new and distinct *GH1* variants have been identified (see outstanding Official Action, page 4), the method also identified 71 polymorphisms in

the *GH1* gene region which are not associated with GH dysfunction. The Examiner stated that since many of the alterations identified by the claimed method will constitute polymorphisms, the identification of a difference in the nucleotide sequence alone does not result in identification of a variation in *GH1* associated with GH dysfunction. As a result, the Official Action alleged that the claims do not include any of the critical steps required to distinguish between polymorphism *GH1* variants associated with GH dysfunction.

However, in the interest of advancing prosecution, claims 1-28, 30-41, and 44 have been canceled. New claims 45-60 have been added. New claims 45-60 are directed to a method for detecting a variation in *GH1* effective to act as an indicator of GH dysfunction an individual. The claims have been drafted to more particularly point out that the sequence obtained from a test sample from an individual is compared with a variant set forth in Table 7B in the present specification. Indeed, the claimed method involves a comparison of a test sample with the novel variants shown in Table 7B. Moreover, the claims have been amended to recite steps for determining growth failure.

Applicants have also deleted the references in the claims to Brook CDG and Tanner et al. Indeed, applicants believe that clinicians dealing with defects in growth hormone secretion/function understand growth failure to mean a failure to

reach the designated series of standard heights set forth in publications such as Brook CDG. Clinicians or practitioners working in this field would also be familiar with standard height charts to measure growth such as TANNER et al. Indeed, applicants believe that one of ordinary skill in the art would use such publications and standards on a daily basis and that the claimed invention is enabled by the present disclosure.

The outstanding Official Action rejected claims 21-22, and 24-27 because the claims required a comparison of a test nucleic acid with a nucleic acid which "was not detected by methods used hitherto, such as those relying on patient selection criteria based primarily on absolute height". The Official Action alleged that the claims do not clearly characterize the structure of the nucleic acid which met the above-identified criteria. However, as noted above, claims 21-22, and 24-27 have been canceled and new claims 45-60 have been added. It is believed that claims 45-60 have been drafted in a manner so as to obviate this rejection.

Thus, in view of the above, it is believed that the claimed invention is supported by an enabling disclosure. As a result, applicants respectfully request that the rejection under 35 USC 112, first paragraph, be withdrawn.

In the outstanding Official Action, claims 1-11 and 21-27 were rejected under 35 USC 112, second paragraph, as allegedly

being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

As noted above, claims 1-11, and 21-27 have been canceled. It is believed to be apparent that new claims 45-60 have been drafted in a manner so as to obviate the contention that the claims of the present application are indefinite.

In the outstanding Official Action, claims 1-6, 10, and 21-25 were rejected under 35 USC 102(b) as allegedly being anticipated by KAMIJO. It is believed that the present amendment obviates this rejection.

As noted above, claims 1-28, 30-41 and 44 have been canceled. New claims 45-60 have been added. Indeed, the claims have been drafted in a manner so as to recite the novel variants of the present application. As KAMIJO fails to disclose or suggest any of these variants, it is believed that KAMIJO fails to anticipate the claimed invention.

Claims 1-16, 10, and 21-25 were rejected under 35 USC 103(a) as allegedly being unpatentable over KAMIJO in view of TANNER. It is believed that the present amendment obviates this rejection.

In imposing the rejection, the Examiner states that KAMIJO does not teach measuring growth failure by evaluating the estimated target adult height, the height of the individual, and

the height of the individual's parents. In an effort to remedy this deficiency, the outstanding Official Action cites to TANNER. However, TANNER fails to disclose the claimed variants. Thus, TANNER fails to remedy the deficiencies of KAMIJO. As a result, the proposed combination of KAMIJO in view of TANNER fails to render obvious the claimed invention.

Claims 6, 7, and 10 were rejected under 35 USC 103(a) as allegedly being unpatentable over KAMIJO or KAMIJO in view of TANNER and further in view of MIYATA. It is believed this rejection has been obviated by the present amendment.

As noted above, KAMIJO and TANNER fail to disclose or suggest the claimed variants. While the outstanding Official Action alleges that MIYATA teaches a method for detecting the presence of genetic variation in the *GH1* gene, MIYATA also fails to disclose the claimed variants. Thus, it is believed that the proposed combination fails to render obvious the claimed invention.

Claim 8 was rejected under 35 USC 103(a) as allegedly being unpatentable over KAMIJO or KAMIJO in view of TANNER and further in view of JIN. This rejection is respectfully traversed.

The outstanding Official Action alleged that KAMIJO or KAMIJO in view of TANNER taught analyzing *GH1* gene for the presence of genetic variation. However, the outstanding Official

Action stated that the references do not also teach analyzing human growth hormone locus control for the presence of genetic variation.

In an effort to remedy the deficiencies of the KAMIJO and TANNER publications, the outstanding Official Action cites to JIN. However, JIN is directed to the complete sequence of a growth hormone locus control region and does not disclose or suggest the variants as set forth in the claimed invention. As a result, JIN fails to remedy the deficiencies of the KAMIJO and TANNER publications. The proposed combination fails to render obvious the claimed invention.

Claim 9 was rejected under 35 USC 103(a) as allegedly being unpatentable over KAMIJO or KAMIJO in view of TANNER and further in view of O'DONOVAN. It is believed that the present amendment obviates this rejection.

In imposing the rejection, the outstanding Official Action cites to O'DONOVAN. The outstanding Official Action contends that O'DONOVAN teaches that DHPLC is a highly sensitive, rapid, automatable and effective means for screening mutations in a large number of sequences. Moreover, the outstanding Official Action further alleges that the O'DONOVAN publication teaches methods for performing DHBLC.

In view of the teachings of O'DONOVAN, it is believed to be apparent that O'DONOVAN fails to teach the variants set

forth in the claimed invention. Thus, it is believed that the O'DONOVAN publication fails to remedy the deficiencies of the KAMIJO and TANNER publications and that the proposed combination of KAMIJO or KAMIJO in view of TANNER and further in view of O'DONOVAN does not render obvious claim 9.

Claim 11 was rejected under 35 USC 103(a) as allegedly being unpatentable over KAMIJO or KAMIJO in view of TANNER, each further in view of MIYATA, as applied to claims 6, 7, and 10, and further in view of CHEN. It is believed that this rejection has been rendered moot by the present amendment.

Upon reviewing the above-identified publications, it is believed to be apparent that none of the publications, alone or in combination with each other, disclose or suggest a method for detecting a variation in *GH1* effective to act as an indicator of GH dysfunction in an individual with the variants as set forth in the claimed invention. Thus, it is believed that the proposed combination fails to render obvious claim 11.

Finally, claims 26 and 27 were rejected under 35 USC 103(a) as allegedly being unpatentable over KAMIJO or KAMIJO in view of TANNER, each further in view of HACIA. It is believed the present amendment obviates this rejection.

The outstanding Official Action alleges that the publications of KAMIJO and TANNER teach analyzing the *GH1* gene for the presence of genetic variation by performing PCR and then

sequencing the amplified DNA or analyzing the amplified DNA by restriction enzyme analysis. However, the outstanding Official Action states that the combined references do not teach assaying for genetic variation by using microarrays comprising probes to a *GH1* gene.

The Official Action believes that HACIA teaches methods for simultaneously detecting the presence of genetic variation of a gene. However, applicants note that HACIA fails to disclose the variants as set forth in the claimed invention. Thus, the proposed combination fails to disclose or suggest the claimed invention. Applicants respectfully request that the rejection be withdrawn.

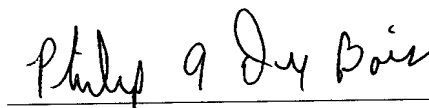
In view of the present amendment and the foregoing remarks, therefore, it is believed that this application is now in condition for allowance, with claims 45-60, as presented. Allowance and passage to issue on that basis are accordingly respectfully requested.

The Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any

overpayment to Deposit Account No. 25-0120 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17.

Respectfully submitted,

YOUNG & THOMPSON



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AMENDMENTS TO THE SPECIFICATION:

Please replace the paragraph beginning at page 38, line 18 , with the following rewritten paragraph:

--A one-tenth volume (5µl) of the reaction mix was analysed on a 0.8% agarose gel to determine that the reaction had worked before denaturing high-pressure liquid chromatography (DHPLC) was performed on a WAVE™ DNA fragment analysis system (Transgenomic Inc. Crewe, Cheshire, UK). To enhance heteroduplex formation, the PCR product was denatured at 95°C for 5 minutes, followed by gradual re-annealing to 50°C over 45 minutes. Products were loaded on a DNAsep column (Transgenomic Inc.) and eluted with a linear acetonitrile (BDH Merck) gradient of 2%/min in a 0.1M triethylamine acetate buffer (TEAA pH 7.0), at a constant flow rate of 0.9ml/minute. The start and end points of the gradient were adjusted according to the size of the PCR product. Analysis took 6.5-8.5 minutes per amplified sample, including the time required for column regeneration and equilibration. Samples were analysed at the Melt temperatures (TM) determined using the DHPLCMelt software ~~(http://insertion.stanford.edu/melt.html)~~ and listed in Table 6. Eluted DNA fragments were detected by an UV-C detector (Transgenomic Inc.).--